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November 15, 2004

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Mail Stop: Appeal Brief-Patents

Re: U.S. Utility Patent Application
Application No. 09/380,203; § 371 Date: April 25, 2000
For: **Transgenic Animals and Cell Lines for Screening Drugs Effective for the Treatment or Prevention of Alzheimer's Disease**
Inventors: de la Monte *et al.*
Our Ref: 0609.4370001/RWE/FRC

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Fee Transmittal Form (PTO/SB/17);

2. Reply Brief Under 37 C.F.R. § 41.41;

3. Request for Oral Hearing Before the Board of Patent Appeals and Interferences;

4. Credit Card Payment Form (PTO-2038) in the amount **$150.00** to cover the request for oral hearing fee; and

5. Return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham
Attorney for Appellants
Registration No. 50,437

FRC/pcd
Encls.

334241v1

PTO/SB/17 (10-04v2)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2005

Effective 10/01/2004. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 150.00

Complete if Known	
Application Number	09/380,203
Filing Date	April 25, 2000
First Named Inventor	Suzanne de la Monte
Examiner Name	Whiteman, B.
Art Unit	1635
Attorney Docket No.	0609.4370001/RWE/FRC

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☒ Credit card ☐ Money Order ☒ Other ☐ None

☐ Deposit Account: ****Charge any deficiencies or credit any overpayments in the fees to Deposit Acct. No. 19-0036.**

Deposit Account Number: 19-0036

Deposit Account Name: Sterne, Kessler, Goldstein & Fox P.L.L.C.

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	790	2001	395	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	44	Independent claims in excess of 3
1203	300	2203	150	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	430	2252	215	Extension for reply within second month	
1253	980	2253	490	Extension for reply within third month	
1254	1,530	2254	765	Extension for reply within fourth month	
1255	2,080	2255	1,040	Extension for reply within fifth month	
1401	340	2401	170	Notice of Appeal	
1402	340	2402	170	Filing a brief in support of an appeal	
1403	300	2403	150	Request for oral hearing	150.00
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,370	2453	685	Petition to revive - unintentional	
1501	1,370	2501	685	Utility issue fee (or reissue)	
1502	490	2502	245	Design issue fee	
1503	660	2503	330	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 150.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Frank R. Cottingham	*Registration No. (Attorney/Agent)*	50,437	*Telephone*	(202) 371-2600
Signature	Frank R. Cottingham			*Date*	NOV. 15, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

de la MONTE *et al.*

Appl. No. 09/380,203

§ 371 Date: April 25, 2000

For: **Transgenic Animals and Cell Lines for Screening Drugs Effective for the Treatment or Prevention of Alzheimer's Disease**

Confirmation No.: 2325

Art Unit: 1635

Examiner: Whiteman, B.

Atty. Docket: 0609.4370001/RWE/FRC

Reply Brief Under 37 C.F.R. § 41.41

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants filed a Brief on Appeal to the Board of Patent Appeals and Interferences for the above-captioned application on March 11, 2004 and a Revised Brief on April 2, 2004. The appeal is directed to the final rejections of claims 1-3, 5, 6, 10-13, 35 and 44-47 under 35 U.S.C. § 112, first paragraph, as set forth in the Office Action dated September 15, 2003. The Examiner's Answer was mailed September 14, 2004. In reply to the Examiner's Answer, Appellants submit this Reply Brief Under 37 C.F.R. § 41.41.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph -- Written Description

The Examiner has withdrawn the written description rejection for claims 11 and 35, and has maintained the written description rejection for claims 1, 2, 3, 5, 6, 10, 12 and 13. *See* Examiner's Answer, page 3. Claim 1 is directed to a DNA construct which

comprises the DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto, wherein the DNA molecule is under control of a heterologous neuro-specific promoter, and wherein the DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. Claim 35 depends from claim 1 and specifies that the activity of AD7c-NTP is selected from the group consisting of neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and irregular swollen neurites. With respect to claim 1, the Examiner stated that:

> claim 1 recites *an activity* of AD7c-NTP when over-expressed in neuronal cells. The activity in claim 1 is broader than the activities observed in the *in vitro* example in the specification as filed and set forth in claim 35. The specification does not teach what nucleotides of a DNA molecule which is at least 90% homolog[ous] to SEQ ID NO: 1 codes for a protein that [has] *an activity* [of] AD7c-NTP when over-expressed in neuronal cells; for example, there is no structure-function relationship regarding putative DNA molecules encoding AD7c-NTP and having the ability to have *an activity* [of] AD7c-NTP when over-expressed in neuronal cells. There is no description in the instant specification concerning what sequences/structures/domains within the protein are necessary for an activity of AD7c-NTP when over-expressed in neuronal cells. In the absence of a description of what sequences/structures/domains are absolutely required for the protein to have *an activity* [of] AD7c-NTP when over-expressed in neuronal cells, the skilled artisan cannot envision what DNA molecules have at least 90% homology to SEQ ID NO: 1. Therefore, functional descriptions alone, as recited in claim 1, do not provide any structural information relating to what the recited nucleotide sequences are from claims only reciting such.

Examiner's Answer, page 11, line 10, through page 12, line 2 (emphasis in original).

Appellants respectfully disagree with the Examiner's assessment. The Examiner has acknowledged that the specification provides adequate description for DNA

molecules that are at least 90% homologous to SEQ ID NO: 1 and that code for a protein that causes neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibriliary tangles, or irregular swollen neurites when over-expressed in neuronal cells. Applicants submit that the specification provides adequate description for the full range of activities of AD7c-NTP when over-expressed in neuronal cells, not just those recited in claim 35.

In addition to the exemplary activities of AD7c-NTP recited in claim 35 (neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and irregular swollen neurites), the specification describes other activities of AD7c-NTP when over-expressed in neuronal cells. For instance, it is noted that over-expression of AD7c-NTP in neuronal cells resulted in *lower densities of viable cells* in culture. *See* specification, page 46, lines 4-7. The specification also notes that the reduced cell density was caused by increased cell death and an *increase in nuclear p53 expression*, suggesting that the cells death is likely to be mediated by apoptosis. *See* specification at page 46, lines 8-10.

According to the USPTO's guidelines for determining adequacy of written description, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. *See* M.P.E.P. § 2163. Importantly, the USPTO's guidelines note that "[w]hat constitutes a 'representative number' is an inverse function of the skill and knowledge in the art." *See id.*

At the time of the effective filing date of the present application, the level of skill in the art of (a) creating nucleic acid variants, (b) expressing the corresponding polypeptide products, and (c) assessing the polypeptides for biological activity, was very high. *See, e.g.*, Appeal Brief at pages 28-32. Given the teachings in the specification,

one of ordinary skill in the art would easily be able to ascertain whether a DNA molecule that is at least 90% homologous to SEQ ID NO: 1 encodes a polypeptide having *any activity* of AD7c-NTP when overexpressed in neuronal cells. *See* Appeal Brief at pages 32-34.

In view of the high level of skill in the art, the exemplary activities of AD7c-NTP set forth in the specification (neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, irregular swollen neurites, lower cell density and increased nuclear p53 expression) would be considered a "representative number of species" of AD7c-NTP activities. Thus, the specification provides adequate description for DNA molecules that are at least 90% homologous to SEQ ID NO: 1 and that code for a protein that has *an activity* of AD7c-NTP when over-expressed in neuronal cells.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph -- Enablement

A. Enablement Rejection Relating to the Ability of a Person of Ordinary Skill in the Art to Make and Use the DNA Molecules of the Invention

The Enablement rejection is based, in part, on the Examiner's assertion that the specification:

> does not reasonably provide enablement for a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neurospecific promoter, wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

See Examiner's Answer, page 6. In explaining this basis of the rejection, the Examiner has repeatedly asserted that "there is no guidance as to which of the nucleotides of a

DNA molecule having at least 90% homology to SEQ ID NO: 1 may be changed while the protein encoded by the DNA molecule has an activity of AD7c-NTP when over-expressed in neuronal cells." *See* Examiner's Answer, page 17. Thus, the rejection is based on the absence of an identification of the *particular nucleotides* of AD7c-NTP that can be changed to produce a DNA molecule that is 90% homologous to SEQ ID NO: 1 and that encodes a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

According to the Examiner's Answer, "the rejection was based on the Wands Factors and not just whether or not one skilled in the art would require the essential nucleotides to practice the claimed invention." *See* Examiner's Answer, page 19. Appellants note that, despite the assertion that the rejection is based on the "Wands Factors," the only issue that has been discussed in support of the rejection is the supposed necessity of the "essential nucleotides" of SEQ ID NO: 1. A detailed analysis of Wands factors, independent of the supposed need for "essential nucleotides," has not been presented by the Examiner.

All of the reasons presented in support of the enablement rejection ultimately derive from the assumption that, without knowledge of the "essential nucleotides" of SEQ ID NO: 1, a person of ordinary skill in the art would not have been able to obtain DNA molecules that are 90% homologous to SEQ ID NO: 1 and that code for proteins that have an activity of AD7c-NTP when over-expressed in neuronal cells without undue experimentation. As previously noted by Appellants, this is an incorrect assumption. *See, e.g.*, Appeal Brief, pages 35-37.

The Enablement rejection is based on an incorrect and factually unsupported assumption as to the manner by which one of ordinary skill in the art could go about obtaining the DNA molecules of the present invention. The Examiner's reasoning assumes that, to obtain DNA molecules that are 90% homologous to SEQ ID NO: 1 and that have the recited activity, one of ordinary skill in the art would need to known *a priori* which particular nucleotides of SEQ ID NO: 1 can be changed to produce a DNA molecule that is 90% homologous to SEQ ID NO: 1 and that encodes a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. Thus, according to the Examiner's position, a skilled person would have to proceed by making individual, rationally-selected mutations in SEQ ID NO: 1 that were pre-determined to encode a protein having an activity of AD7c-NTP when over-expressed in neuronal cells. As Appellants have previously indicated, this is not how one of ordinary skill in the art, in view of the teachings in the specification, would have gone about making the DNA molecules of the invention.

To make and use DNA molecules that are encompassed by or included within the subject matter of the claims on appeal, a person of ordinary skill in the art could have first obtained DNA molecules that are at least 90% homologous to SEQ ID NO: 1 using, *e.g.*, the methods set forth in the specification at page 19, lines 3-15, or other methods known an available in the art. *See* Appeal Brief, pages 29-31. Once obtained, a person of ordinary skill in the art could have easily tested the DNA molecules having at least 90% homology to SEQ ID NO: 1 for the ability to encode a protein having an activity of

AD7c-NTP when over-expressed in neuronal cells. Such methods are described throughout the specification. *See* Appeal Brief, pages 32-34.

In addressing Appellants' explanation as to how one of ordinary skill in the art would have gone about obtaining the DNA molecules of the invention, the Examiner stated that

> Appellants' argument indicates that one skilled in the art would have to perform trial and error experimentation on each mutated version of SEQ ID NO: 1 to determine which mutated version of SEQ ID NO: 1 has an activity of AD7c-NTP when over-expressed in neuronal cells. See MPEP 2164.05(a), which recites that the specification must be enabling [as] of the filing date. Thus, if the guidance in the specification requires one skilled in the art to perform trial and error experimentation on each mutated version of SEQ ID NO: 1 to determine which version meets the structural limitation of the claims, this would indicated that the specification was not enabling as of the filing date.

See Examiner's Answer, page 20. Apparently, the Examiner's position is that trial and error experimentation necessarily indicates lack of enablement. The proper legal standard, however, is not whether the practice of an invention would require "trial and error," but whether the amount of experimentation needed would be regarded as "undue" from the perspective of one of ordinary skill in the art. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Experimentation, even complex experimentation, is not undue if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

The Examiner has not presented any evidence to indicate that making DNA molecules that are at least 90% homologous to SEQ ID NO: 1, and testing them for the ability to encode proteins that have an activity of AD7c-NTP when over-expressed in neuronal cells, would be regarded as undue experimentation by persons of ordinary skill in the art. Appellants have put forth evidence and sound scientific arguments indicating that such screening processes would have been regarded as routine. *See* Appeal Brief, pages 28-34. The enablement rejection therefore cannot be maintained based on the Examiner's unsupported assertion that one of ordinary skill in the art would have had to engage in "trial and error experimentation" to make and use the claimed invention.

B. Enablement Rejection Relating to the Ability of a Person of Ordinary Skill in the Art to Practice the Methods of the Invention

With respect to the method claims, the Examiner has maintained the enablement rejection on the grounds that the DNA molecules used in the methods are under the control of a heterologous neuro-specific promoter, and that:

> if the result of the candidate drug in any of the detection steps is caused by interacting with the promoter, one skilled in the art would have to further experiment without guidance from the specification or prior art to determine whether the promoter is associated with a disease recited in the claims.

Examiner's Answer, page 22.

Appellants again point out that the claims are directed to methods for screening *candidate* drugs that are *potentially* useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas or glioblastomas. To identify such *candidate* drugs, there is no need to "determine whether the promoter is associated

with a disease recited in the claims." Although it may be useful to perform additional testing on the candidate drugs identified by the practice of the claimed methods to confirm their clinical efficacy, such additional testing is outside the scope of the present claims. Thus, whether or not such additional testing would amount to undue experimentation, which is apparently the crux of the Examiner's enablement rejection, is irrelevant with respect to the enablement of the methods encompassed by the present claims. A drug that suppresses or prevents the expression of the protein coded for by the DNA construct of the specified host cell, even if it does so by interacting with the heterologous neuro-specific promoter, is a "candidate drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas or glioblastomas." The Examiner has not presented any evidence or sound scientific reasoning to indicate otherwise.

III. Conclusion

In light of the arguments above, as well as those set forth in Appellants' Brief on Appeal filed April 2, 2004, Appellants respectfully submit that the final rejections of claims 1-3, 5, 6, 10-13, 35 and 44-47 under 35 U.S.C. § 112, first paragraph, are improper and should be reversed.

Respectfully submitted,

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Date: NOV. 15, 2004

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